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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/816,099 | 03/31/2004 | Katalin Varadi | P-279.00 | 9454 |

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| EXAMINER | |
|---|---|
| KOSSON, ROSANNE | |
| ART UNIT | PAPER NUMBER |
| 1653 | |

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/816,099 | POKHARNA ET AL. | |
| | Examiner | Art Unit | |
| | Rosanne Kosson | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8 and 10-23* is/are pending in the application.

4a) Of the above claim(s) *14-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 20, 2006 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims have been amended or added. Claim 9 has been canceled. Accordingly, claims 1-8, 10-13, 22 and 23 are examined on the merits herewith.

***Claim Rejections - 35 USC § 103***

Claims 1-8, 1-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et a. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). This rejection was discussed in the previous Office actions.

Applicants assert that the claimed invention is not obvious, because the combination of the cited references not does teach or suggest a lyophilized mixture comprising $CaCl_2$ and a fluorescently labeled thrombin substrate that forms a clear solution when dissolved in an aqueous solution. Applicants assert that the references do not teach that the substrates are lyophilized with $CaCl_2$ and that they teach that these two components are used separately, each added from its own stock solution when an assay is performed. Applicants cite portions of Wöber et al., Váradi et al. and Lawson et al.

In reply, the rejection is one of obviousness, not of anticipation. As previously discussed, it the combination of the cited references that suggests this lyophilized preparation. Váradi et al. and Lawson et al. teach that their substrates are available as dry powders that are soluble with calcium chloride in the buffers used in a thrombin generation assay. Thus,

lyophilized forms of these powders may also be prepared. Hawkins et al. teach the advantages of lyophilized reagents in clinical assays- they reduce bulk in the packaged form and improve reagent stability (see col. 1, lines 43-50, and col. 2, lines 56-65). Hogan et al. teach that, in a diagnostic kit, or when performing an assay with a diagnostic kit, the reagents may be premixed before lyophilization so that, when reconstituted, a complete mixture is formed with the reagents in the proper ratio and ready for use (see col. 37, lines 14-29). Combining the substrate and the cofactor ($CaCl_2$) reduces the number of pipetting steps, thereby reducing the chance of assay errors due to pipetting errors, and reduces the number of assay steps, allowing the assay to be performed faster. Regarding Lawson et al., the section referred to by Applicants and the preceding paragraph (p. 4836, right col., second and third full paragraphs) discloses that the thrombin substrate is prepared in DMSO as a stock solution. But, the working solution for all the assays contains 1 μM thrombin substrate in TBS (Tris-buffered saline solution), an aqueous solution. For the factor VIIa assays, a working solution of HBS (HEPES-buffered saline solution) containing 5 mM $CaCl_2$ and 1 μM thrombin substrate is prepared.

Regarding Váradi et al., the section referred to by Applicants (p. 2375, second full paragraph, presumably in the right col.) discloses that, to perform the assay, 10 μL of TF/PL in TBS is mixed with 50 μL of a solution containing 1 mM fluorescently labeled thrombin substrate and 15 mM $CaCl_2$, plus 40 μL of FVIII inhibitor plasma. The reference does not explicitly state what the thrombin substrate and calcium chloride are dissolved in, but the final assay mixture is an aqueous solution of at least 40% plasma and 10% TBS. The reference does not indicate that any precipitate forms or that the assay reagents or mixtures have any solubility problems.

Thus, Lawson et al. and Váradi et al. teach that $CaCl_2$ and a fluorescently labeled thrombin substrate are used together as an assay reagent and are soluble together in an aqueous solution. Hogan et al. provide the motivation for combining assay reagents and

lyophilizing them, and Hawkins et al. also provide motivation for preparing lyophilized assay reagents. This combination of cited references, therefore, teaches all the limitations of the claimed invention.

Applicants assert that their substrates are insoluble in aqueous solution and that when their substrates are mixed with $CaCl_2$ in aqueous solution, a precipitate forms. Applicants assert that a skilled artisan would have no motivation to lyophilize this suspension, because she would not expect to be able to dissolve the lyophilized solids to form a clear solution for use in an assay. Applicants further assert that because the thrombin substrates described in the references are available as dry powders, there would be even less motivation to lyophilize a mixture of the substrate and calcium chloride, and there would be no reason to do so, because the skilled artisan would expect a precipitate to form when trying to prepare an aqueous solution. Additionally, Applicants assert that one of ordinary skill in the art would be motivated to use separate solutions of each reagent, because lyophilization is involved and time-consuming and requires specialized equipment and because he or she would not recognize any advantage of lyophilizing the substrate with calcium chloride. The cited references disclose no benefit that would result from this additional step. Lastly, Applicants assert that one of ordinary skill in the art would have no reasonable expectation of success in combining the references, because combining a fluorescently labeled thrombin substrate and calcium chloride in an aqueous solution produces a precipitate, and upon reconstituting a lyophilized preparation of this mixture, a precipitate would result, not an aqueous solution.

In reply, Applicants appear to state that their invention does not work. An invention that does not work (is inoperative) lacks utility. But, as discussed previously and above, Lawson et al. and Váradi et al. teach that the fluorescently labeled thrombin substrate and calcium chloride

may be dissolved and used together in an aqueous solution without the formation of a precipitate. Thus, one of ordinary skill in the art at the time that the invention was made would have had every expectation that the combination of the cited references described above, a kit and a method of using the kit to measure thrombin generation, would have worked for this intended purpose. Motivation for combining the references has been provided previously and above. To reiterate, lyophilization of the substrate-calcium chloride solutions of Lawson et al. and Váradi et al. provides a stable, easily packaged kit reagent that, when used in an assay, allows the assay to be performed more quickly and more accurately than when each reagent is used separately. Thus, a lyophilized substrate-calcium chloride reagent has several advantages. In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1653

rk/2006-08-22

MARYAM MONSHIPOURI, PH.D.
PRIMARY EXAMINER